

Japanese Surveillance of Neuroendovascular Therapy in JR-NET - Part II. Japanese Registry of NeuroEndovascular Treatment 3. Main Report

Nobuyuki SAKAI,¹ Kazutaka UCHIDA,² Koji IIHARA,³ Tetsu SATOW,⁴ Masayuki EZURA,⁵ Akio HYODO,⁶ Shigeru MIYACHI,⁷ Susumu MIYAMOTO,⁸ Yoji NAGAI,⁹ Kunihiro NISHIMURA,¹⁰ Kazunori TOYODA,¹¹ Shinichi YOSHIMURA,² Hirotoshi IMAMURA,¹ Chiaki SAKAI,² Yuji MATSUMARU,¹² and Japanese Registry of Neuroendovascular Therapy (JR-NET) investigators

¹Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan;

²Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan;

³Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka, Japan;

⁴Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan;

⁵Department of Neurosurgery, National Hospital Organization Sendai Medical Center, Sendai, Miyagi, Japan;

⁶Department of Neurosurgery, Dokkyo University Saitama Medical Center, Koshigaya, Saitama, Japan;

⁷Neuroendovascular Therapy Center, Aichi Medical University, Nagakute, Aichi, Japan;

⁸Department of Neurosurgery, Graduate School of Medicine, Kyoto University, Kyoto, Kyoto, Japan;

⁹Clinical and Translational Research Center, Kobe University Hospital, Kobe, Hyogo, Japan;

¹⁰Department of Preventive Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan;

¹¹Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan;

¹²Department of Neurosurgery, University of Tsukuba, Tsukuba, Ibaraki, Japan

Abstract

This study, following Japanese Registry of NeuroEndovascular Treatment 1 and 2 (JR-NET 1 & 2), shows an annual trend of cases including adverse events and clinical outcomes at 30 days after NET. JR-NET3 was registered by 749 cumulative total number of physicians, certified by the Japanese Society of Neuroendovascular Therapy in 166 centers, between 2010 and 2014. Medical information about the patients was anonymized and retrospectively registered through a website. A total of 40,177 patients were recruited, 632 patients were excluded because data of preprocedural status were not available. So we analyzed 39,545 patients retrospectively. The proportion of octogenarians is increasing year-by-year and 14.7% in 2014 compared with 10.4% in 2010. Most frequent target disease is intracranial aneurysm. For the proportion of the treatment of intracranial aneurysm, 50.0% in 2010, but that has decreased to 44.8% in 2014. However, number of procedures were increased from 3150 in 2010 to 3419 in 2014. Although before the positive clinical evidence of mechanical thrombectomy for acute ischemic stroke (AIS) was established, the proportion of endovascular treatment for AIS increased 13.8% in 2014 compared with 6.3% in 2010. The number of patients requiring neuroendovascular treatment in Japan is increasing since 2010–2013, but that declined a little in 2014 caused by study operation suspended at the end of 2013. The outcomes of such therapy are clinically acceptable. Details of each type of treatment will be investigated in sub-analyses of the database.

Key words: nationwide surveillance, endovascular treatment, registry study, clinical outcome, safety endpoint

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Introduction

Recently, minimally invasive treatment is widely spreading, especially neuroendovascular therapy (NET) is progressing steadily due to advances in devices and increasing certified physicians in Japan. The Japanese Society of NET (JSNET) has certified physicians that consists of 1222 specialists, including 303 senior trainers on April 1, 2018, and it is an indispensable license to treat various cerebrovascular diseases such as cerebral aneurysm, supra-aortic artery stenosis/occlusion, arteriovenous shunts, and acute stroke. The Japanese Registry of NeuroEndovascular Treatment (JR-NET) study group endorsed by JSNET have been conducted an implemented retrospective studies [JR-NET 1 and 2 (JR-NET 1 & 2)]¹⁾ to clarify the general status of NET delivered by JSNET-certified physicians. In this study (JR-NET 3), clinical and procedural data were retrospectively collected from January 2010 through December 2014. In 2015, it was a year of dramatically change at NET in Japan, because the usefulness of NET for acute ischemic stroke (AIS) was established,²⁻⁶⁾ and flow diverter⁷⁾ was approved for unruptured large or giant aneurysm of the internal carotid artery. However, this study's period was till 2014. The study aimed to determine annual changes in neuroendovascular treatment modalities and in major adverse events within 30 days in the same way as JR-NET 1 & 2.

Materials and Methods

Study design

JR-NET3 (2010–2014): This was the third nationwide surveillance of neuroendovascular treatments in Japan. The registry targeted all patients treated by JSNET board certified physicians between January 2010 and December 2014, except for those whom their physicians judged unsuitable for this registry. Medical information about the patients was anonymized and retrospectively registered through a website (<https://jr-net.tri-kobe.net/jr-net/>). Data were collected at the Translational Research Informatics Center (TRI, <http://www.tri-kobe.org/>). The study protocol, which is summarized briefly here, is available online with the full text of this article (<https://www.jrnet.umin.jp/>). All members of the writing committee assumed responsibility for the accuracy and completeness of the data and for the fidelity of the study with regard to the protocol.

Patients

All patients treated by neuroendovascular treatment at participating centers during the study period were

basically enrolled in the study. The local institutional review boards at each institution approved the study protocol before the investigators proceeded with the study.

Primary and secondary endpoints

The primary endpoint was activities of daily life (ADL) determined according to Modified Rankin Scale (mRS) scores.⁸⁾ The secondary endpoints comprised the technical success of procedures and major adverse events that occurred within and at 30 days after procedures. A score of 0 on the mRS indicates no disability, whereas scores of 1 or 2 indicate slight disability (some help required with ADL but basically independent), scores of 3–5 indicate moderate disability (some help required with ADL) to severe disability (bedridden or constant specific care required), and a score of 6 indicates death.

Adverse events were classified as minor and major when mRS scores deteriorated by 1 and ≥ 2 points, respectively. That are same in previous surveillance.¹⁾

Statistical analysis

Data were statistically analyzed using JMP 13 software (SAS Institute, Cary, NC, USA). The statistical significance of intergroup differences was assessed using the *t*-test for quantitative scales, Pearson's χ^2 test; $P < 0.05$ was considered as significant.

Results

Backgrounds and characteristics of patients

A total of 40,177 patients were recruited, 632 patients were excluded because data of preprocedural status were not available. So we analyzed 39,545 patients (mean age, 65.1 ± 14.1 years; female, 48.8%) in this study (Table 1), which involved 749 cumulative total number of board-certified physicians at 166 centers in JR-NET3 (Appendix). Figure 1 shows the proportions of treated patients within various age groups. Although patients aged between 40 and 70 years were the main recipients of treatment, the rates of octogenarians increased annually from 10.4% in 2010 to 14.7% in 2014 ($P < 0.001$), whereas the ratio of younger patients (<40 years) remained constant ($P = 0.203$). In the annual transition of the number of cases peaked in 2013 and declined in 2014.

Procedures

Among a total 39,545 procedure neuroendovascular procedures implemented between 2010 and 2014. The proportion of treatment for aneurysms were 46.1%, angioplasty for carotid 22.5%, angioplasty for others 10.5%, embolization of brain and

Table 1 Annual trends of JR-NET3 data

	2010	2011	2012	2013	2014	Total
Total number	<i>n</i> = 6794	<i>n</i> = 7292	<i>n</i> = 8348	<i>n</i> = 8924	<i>n</i> = 8095	<i>n</i> = 39,545
Age	64.8 ± 14.0	64.8 ± 14.0	65.3 ± 14.0	65.3 ± 14.2	65.8 ± 14.2	65.1 ± 14.1
Female	3321 (48.9%)	3515 (48.2%)	4146 (49.7%)	4322 (48.4%)	3984 (49.2%)	19,288 (48.8%)
mRS before treatment	0.46	0.46	0.50	0.48	0.48	0.48
Procedures	<i>n</i> = 6305	<i>n</i> = 6848	<i>n</i> = 7811	<i>n</i> = 8402	<i>n</i> = 7626	<i>n</i> = 36,992
Aneurysm treatment	3150 (50.0%)	3158 (46.1%)	3683 (48.4%)	3883 (46.2%)	3419 (44.8%)	17,293 (46.7%)
Dome embolization, ruptured	1092 (17.3%)	1089 (15.9%)	1262 (16.2%)	1308 (15.6%)	1184 (15.5%)	5935 (16.0%)
Dome embolization, unruptured	1811 (28.7%)	1840 (26.9%)	2181 (27.9%)	2279 (27.1%)	2009 (26.3%)	10,120 (27.4%)
Dissection/parent artery occlusion	248 (3.9%)	229 (3.3%)	240 (3.1%)	296 (3.5%)	226 (3.0%)	1239 (3.3%)
Angioplasty/stenting	1882 (29.8%)	2039 (29.8%)	2234 (28.6%)	2397 (28.5%)	2063 (27.1%)	10,615 (28.7%)
Carotid artery	1518 (24.1%)	1605 (23.4%)	1775 (22.7%)	1948 (23.2%)	1655 (21.7%)	8501 (23.0%)
Vertebral/subclavian artery	164 (2.6%)	198 (2.9%)	214 (2.7%)	197 (2.3%)	175 (2.3%)	948 (2.6%)
Intracranial artery	200 (3.2%)	236 (3.4%)	245 (3.1%)	252 (3.0%)	233 (3.1%)	1166 (3.2%)
Brain & spinal AVM embolization	257 (4.1%)	241 (3.5%)	261 (3.3%)	294 (3.5%)	268 (3.5%)	1321 (3.6%)
DAVF embolization	347 (5.5%)	415 (6.1%)	416 (5.3%)	493 (5.9%)	463 (6.1%)	2134 (5.8%)
Tumor embolization	273 (4.3%)	321 (4.7%)	353 (4.5%)	422 (5.0%)	363 (4.8%)	1732 (4.7%)
Acute stroke treatment	396 (6.3%)	674 (9.8%)	864 (11.1%)	913 (10.9%)	1050 (13.8%)	3897 (10.5%)
Physicians in charge	<i>n</i> = 6791	<i>n</i> = 7289	<i>n</i> = 8348	<i>n</i> = 8921	<i>n</i> = 8093	<i>n</i> = 39,442
Senior trainer, board certified	3689 (54.3%)	3862 (53.0%)	4311 (51.6%)	4738 (53.1%)	4226 (52.2%)	20,826 (52.8%)
Specialist, board certified	2807 (41.3%)	3070 (42.1%)	3623 (43.4%)	3724 (41.7%)	3425 (42.3%)	16,649 (42.2%)
Non-specialist	295 (4.3%)	357 (4.9%)	414 (5.0%)	459 (5.1%)	442 (5.5%)	1967 (5.0%)

spinal arteriovenous malformations (AVMs), dural arteriovenous fistulae (dAVF) 8.9%, and acute stroke 5.9% of procedures, respectively in 2010. Thus, in 2014, the treatment for aneurysm was 42.5%, angioplasty for carotid 20.5%, acute stroke 12.7%, angioplasty for others 9.1%, AVMs/dAVF 9.1%, respectively. The proportion of treatments remained relatively constant, but acute stroke significantly increased from 5.9% in 2010 to 12.7% in 2014 ($P < 0.001$) (Fig. 2).

Elective or emergency procedures The rate of emergency treatment was increasing little-by-little between 32% and 36% throughout the study period (Fig. 3).

Physicians in-charge The proportion of treatment procedures with JSNET senior trainers, specialists, and non-specialist in charge 52.8%, 42.2%, and 5%, respectively remained relatively constant (Table 1).

mRS scores before and after treatment Figures 4A and 4B shows the overall proportions of mRS scores before and after treatment. Before treatment, ≥90% of patients were in relatively good condition, with mRS scores of 0–2 (Fig. 4A). At 30 days after undergoing procedures, the patients maintained mRS scores of 0–2 decreased from 79.4% in 2010 to 76.3% in 2014 (Fig. 4B). **mRS scores after each type of procedure** Figure 5 shows the outcomes of each type of treatment according to mRS scores. Outcomes were favorable for 58.3% and 95.3% of patients with ruptured and unruptured aneurysms, respectively, (mRS 0–2) and for ≥85% those after carotid artery stenting (CAS), vertebral artery (VA)/subclavian artery (SCA), dAVF, and tumors. On the other hand, 75.5%, 71.6%, and only 33.1% of those treated for intracranial artery disease, in AVM, and acute stroke had favorable outcomes.

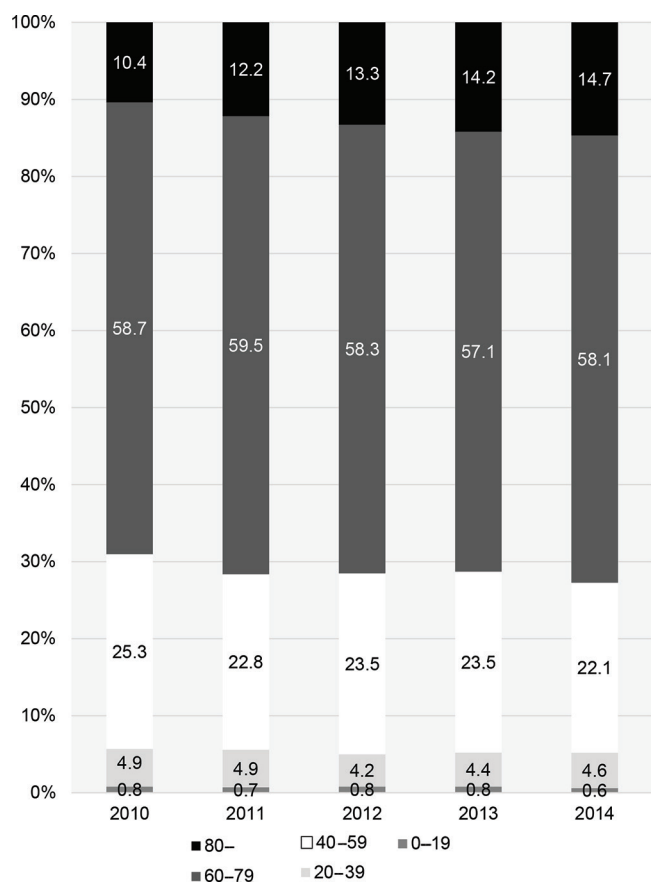


Fig. 1 Annual changes in patients' age during JR-NET3. Rates of octogenarians increased annually from 10.4% in 2010 to 14.7% in 2014 ($P < 0.001$), whereas the ratio of younger patients (<40 years) remained constant ($P = 0.203$). JR-NET3: Japanese Registry of Neuroendovascular Therapy 3.

Procedural complications of each treatment Figure 6 shows the frequency of procedural complications after each type of treatment. Death and major procedural complications occurred in 5.1% and 1.4% of patients treated for ruptured and unruptured aneurysms, respectively.

None of the patients died of procedure-related complications after VA/SCA, and tumors. Major complication and death occurred mostly in acute stroke and ruptured aneurysm which was about 5%. In another procedures, the occurrence of death and major complication was around 1–2%.

Discussion

This study, following JR-NET 1 & 2, shows an annual trend of cases including adverse events and clinical outcomes at 30 days after neuroendovascular therapy. It has huge number of cases, about 40,000 cases, showing the actual state of neuroendovascular

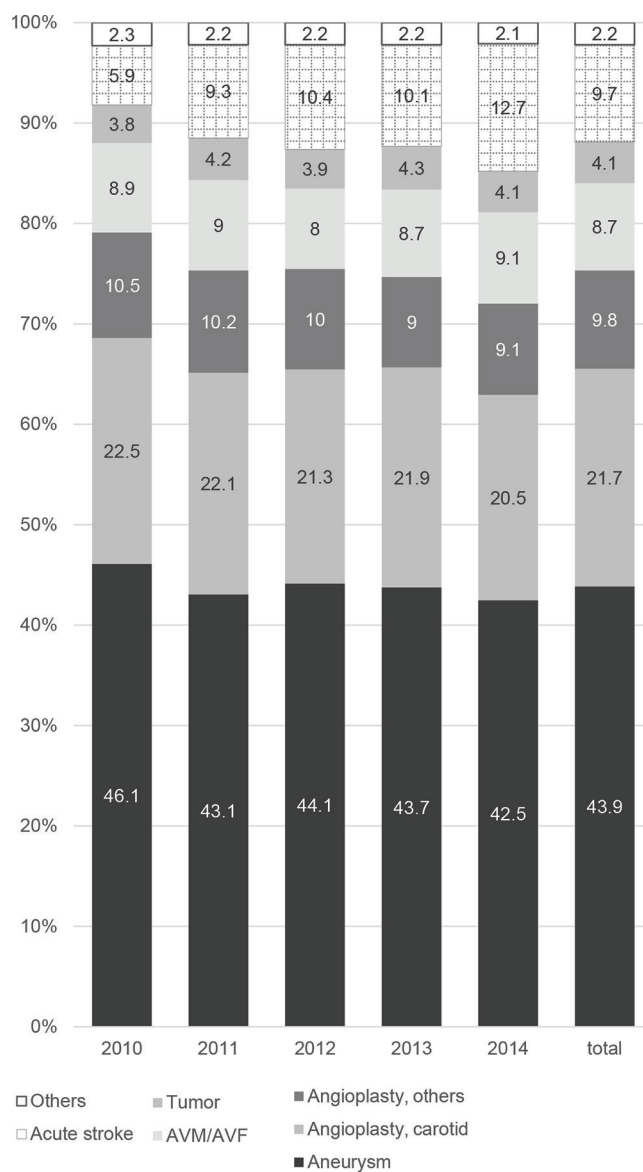


Fig. 2 Annual changes in the types of procedures. The proportion of treatments remained relatively constant, but acute stroke significantly increased from 5.9% in 2010 to 12.7% in 2014 ($P < 0.001$).

therapies in Japan. This study was conducted from 2010 to 2014. Many new devices, Merci V retriever (Stryker Neurovascular, Fremont, CA, USA)^{9,10} and Enterprise VRD (Cerenovus, Johnson and Johnson, New Brunswick, NJ, USA)¹¹ in 2010, Penumbra system (Penumbra, Alameda, CA, USA)¹² in 2011, Neuroform EZ (Stryker Neurovascular)¹³ in 2012, Wingspan stent system (Stryker Neurovascular)¹⁴ in 2013, Solitaire FR (Medtronic Neurovascular, Irvine, CA, USA)¹⁵ and Trevo ProVue retriever (Stryker Neurovascular)¹⁶ in 2014 were started for reimbursement. Thus, it was the beginning of stents for intracranial aneurysm treatment, thrombectomy

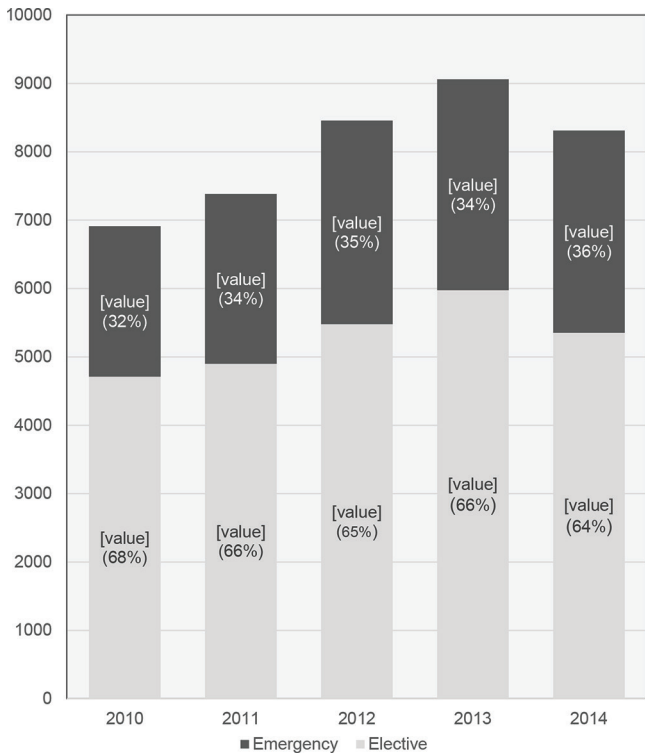


Fig. 3 Number of elective and emergency procedures. The total numbers of elective and emergency procedures increased annually except for 2014, and emergency procedure significantly increased from 31.9% in 2010 to 35.6% in 2014 ($P < 0.001$).

and intracranial stent for ischemic stroke. But, it was before the positive clinical evidence of endovascular treatment for AIS was established,²⁻⁶⁾ and flow diverter stent⁷⁾ was reimbursed. Overall, the proportion of elderly people aged 80 or over has been increasing 14.7% in 2014, and it is doubled even compared with previous survey 7.0% in 2005.¹⁾ This might be caused by the increase in the population of elderly people and the fact that NET is less invasive, which is more likely to be applied to older people.

In the annual trend of the number of cases, it has been increasing steadily until 8402 in 2013, but declined to 7626 in 2014. In addition, emergency cases have been in the range of 32–36%, which is about 5% increase compared with JR-NET 1 & 2. This reflects suggested the increase in acute stroke. The mRS before NET was similar to JR-NET 1 & 2, in which the ratio of mRS 0–2 was 93.3% from the previous 91.3%, but the postoperative mRS deteriorated in which the ratio of mRS 0–2 was 77.2% from the previous 82.5%. It suggested that the cause of the decrease in the percentage of independence after onset due to increase of acute stroke. In this study, the good prognosis of mRS 0–2 at 30 days after the procedure was 33.1%. Endovascular therapy in ischemic stroke with acute large-vessel occlusion: Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2 (RESCUE - Japan

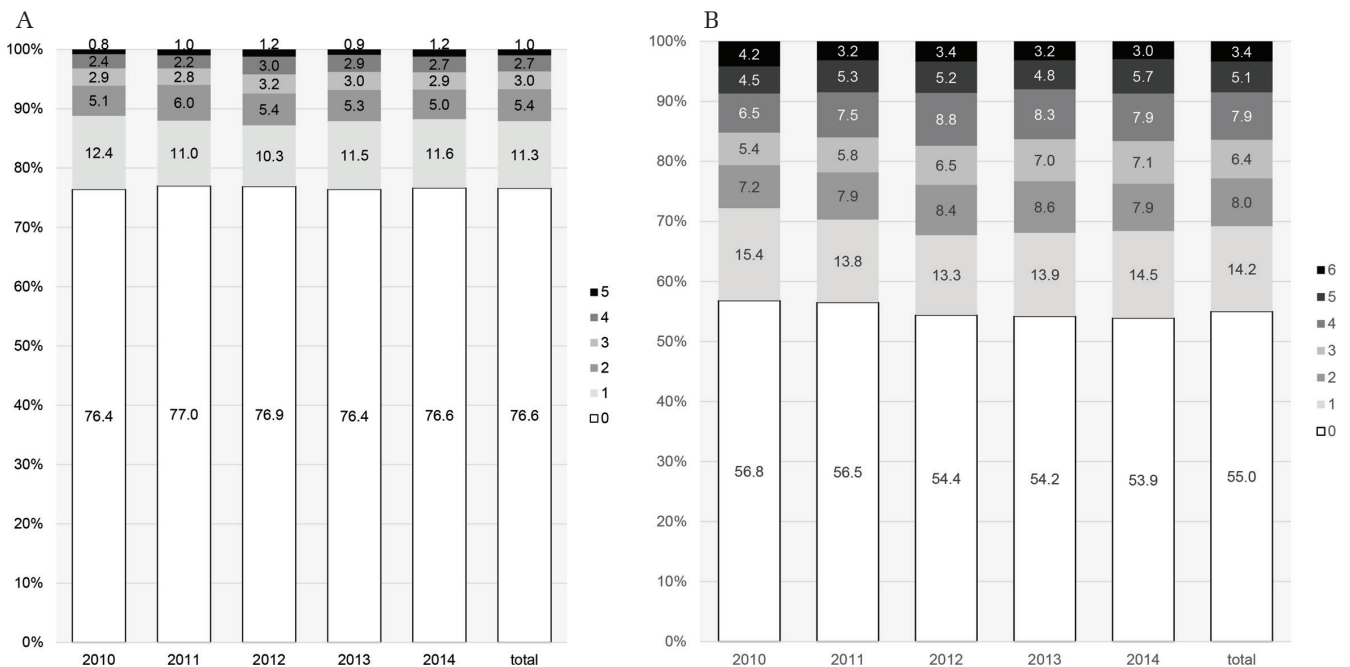


Fig. 4 Proportions of Modified Rankin Scale (mRS) scores before and after procedures. Ratio of patients with mRS 0–2 was $\geq 90\%$ before therapeutic procedures (A), decreased at 30 days thereafter (B), but remained $>75\%$.

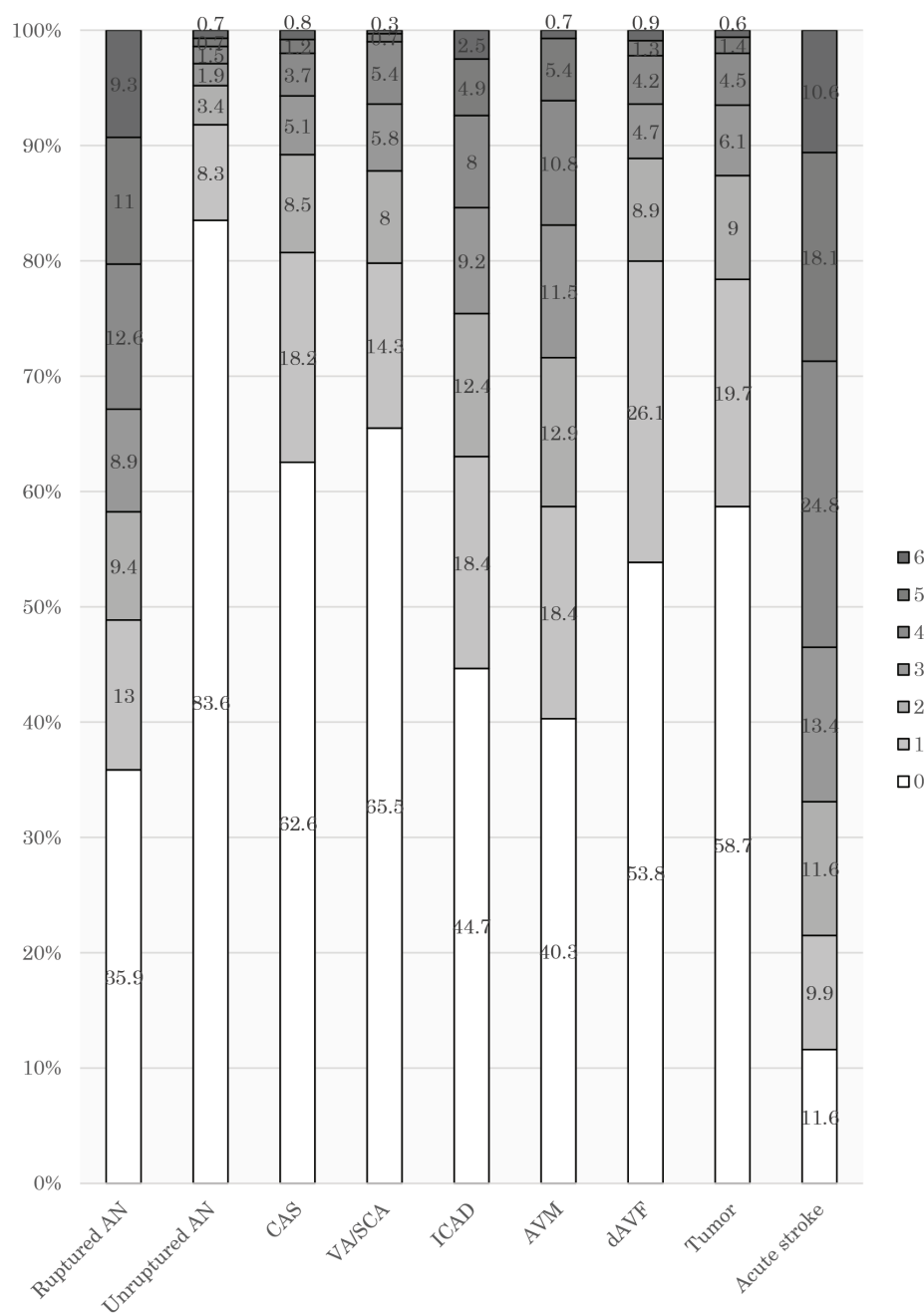


Fig. 5 Proportions of Modified Rankin Scale (mRS) scores at 30 days after various procedures. Outcomes were favorable (mRS 0–2) for 58.3% and 95.3% of patients with ruptured and unruptured aneurysms respectively. Ratios of favorable outcomes of carotid artery stenting, vertebral artery/subclavian artery, dural arteriovenous fistula, and tumor embolization were >85%. On the other hand, the ratios of favorable outcomes were 75.5%, 71.6%, and only 33.1% in intracranial artery disease, arteriovenous malformation and acute stroke, respectively.

Registry 2)¹⁷⁾ showed mRS 0–2 at 90 days after the procedure was 35.1%. The results were similar of them. The minor complication overall increased to 3.5–9.4% compared with JR-NET 1 & 2 (0.7–2.2%), but the ratio of major complication (0.5–3.7%) and death (0–2.4%) has not increased compared with the ratio of major complication (0–2.8%) and

death (0.6–5.8%) in JR-NET 1 & 2. The reason was suggested that asymptomatic, transient ischemia, and high intensity images in magnetic resonance image on diffusion waited image were firmly registered.

A nationwide population-based cohort study in Taiwan showed mortality of subarachnoid hemorrhage after neuroendovascular therapy was 10.4% similar

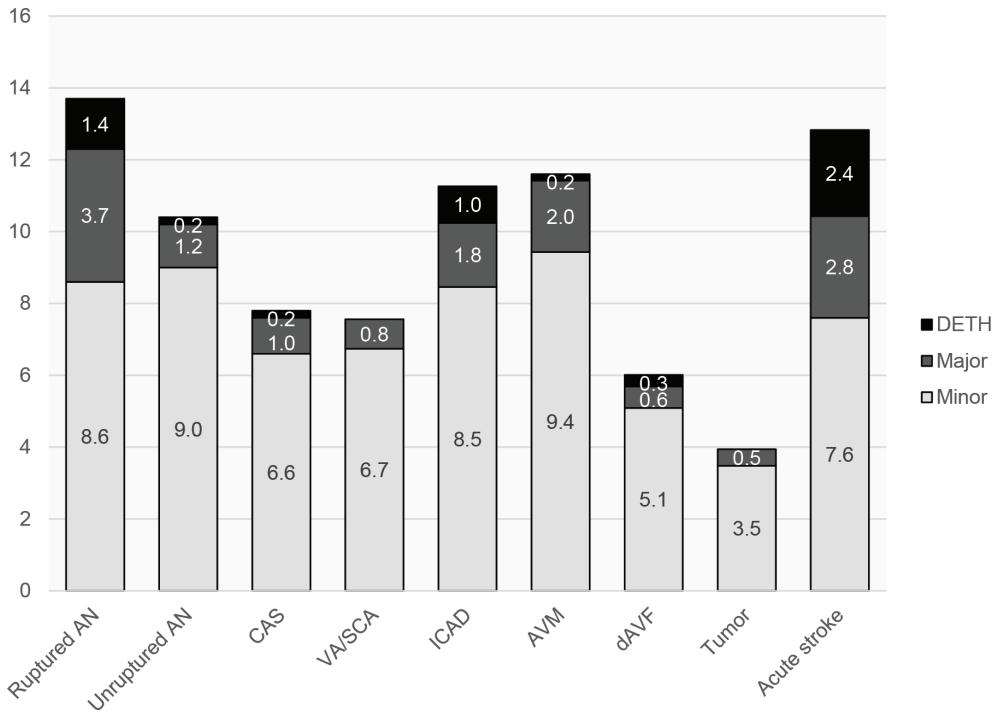


Fig. 6 Complications associated with each procedure. Death and major complication rates were higher after procedures for ruptured aneurysm (5.1%) and acute stroke (5.23%), but less frequent for those that treated dural arteriovenous fistula (0.46%), tumor embolization (0.46%), and vertebral artery/subclavian artery (0.82%).

to 9.3% in this study suggesting identical result in Asian.¹⁸⁾ At 30-day follow-up, mortality after CAS performed by physicians with varied experience and utilizing a formal training program was 1.1%¹⁹⁾ higher than 0.7% in our study ($P = 0.09$).

This study has some limitations. First, this study was retrospective study, and detailed data concerning individual patients were not obtained. Second, this study covered at about 40% of all procedures performed in Japan, and completeness of the survey was insufficient. Finally, this study was registered in Japan, and are consequently, of uncertain generalizability. For the future, JR-NET4 with higher completeness are considered necessary to more precisely clarify the status of NET in Japan.

Conclusion

This study showed NET was certain safety and effective in Japan. This study's period was before establishing the effectiveness of endovascular treatment for acute ischemic stroke in 2015. So it is expected that the number of cases will increase rapidly in the future. Details about each treatment or disease will be assessed in sub-analyses of this database.

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The JR-NET3 Study Group: Co-principal investigator; Nobuyuki Sakai, Kobe City Medical Center General

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Conflicts of Interest Disclosure

All authors who are members and non-members of the Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statements through the website for JNS. Nobuyuki Sakai; UNRELATED: Consultancy: Achieva, Cardiatis, Cerenovus/Johnson and Johnson, Medtronic, Microvention/Terumo, Penumbra, Stryker; Grants; Terumo (research grant). All co-authors have no conflict of interest for this manuscript.

Appendix

Participants, their hospitals, and the number of registered patients in JR-NET3 are listed when >100 patients were registered; names of investigators are listed when <100 patient were registered. N Sakai, H Adachi, Y Ueno, H Yamagami, H Imamura, T Kunieda, M Koyanagi, Y Kuramoto, K Todo, T Ishikawa, T Shigematsu, S Yamamoto, S Sato, K Asai, K Arimura, S Tani, Y Mineharu, O Narumi, A Ishii, C Sakai, H Ikeda, T Kono, Kobe City Medical Center General Hp., 1100; Y Matsumoto, R Kondo, E Furui, I Suzuki, T Takahashi, T Akiyama, H Endo, K Sato, Y Kageyama, S Sawa, K Niizuma, Y Yazawa, R Itabashi, Konan Hp., 1086; M Ezura, N Kimura, K Tsuboi, K Sato, S Nishimura, K Sato, S Osawa, I Suzuki, Sendai Medical Center, 942; K Sugiu, Y Terai, K Tokunaga, A Katsumata, N Kusaka, A Nishida, S Kawada, K Watanabe, T Hishikawa, K Hirashita, H Itami, Okayama Univ., 917; S Ota, Y Sekihara, N Shimizu, K Maeda, Ota Memorial Hp., 900; Y Matsumaru, H Izumoto, W Tsuruta, Y Nakane, H Okumura, M Hayakawa, Y Hirota, M Sato, Y Kamiya, A Watanabe, T Amano, M Aoki, T Hyuga, D Watanabe, K Mori, M Seida, T Osanai, Toranomon Hp., 886; M Hirohata, M Takeuchi, Kurume Univ., 875; M Tsutsumi, K Nii, H Eto, K Kazekawa, H Aikawa, M Onizuka, H Yoshida, K Sakamoto, T Mizokami, H Oishi, M Iko, K Nakai, S Kin, Fukuoka Univ. Chikushi Hp., 785; T Nonaka, Y Yonemasu, A Takahashi, T Onda, S Kogure, R Ueda, T Shimizu, T Nomura, A Yamamura, S Hayashi, Shiroishi Memorial Hp., 751; I Nakahara, M Nakamura, S Furuichi, Y Iwamuro, T Ohta, S Toyota, E Furui, Y Watanabe,

S Matsumoto, R Ishibashi, Y Urabe, M Gomi, Y Fukushima, M Saka, T Nakazawa, Y Matsuda, Kokura Memorial Hp., 702; A Hyodo, Y Hori, M Shirato, K Suzuki, S Suzuki, T Takigawa, N Shimizu, Y Tanaka, I Takano, Dokkyo Medical Univ. Koshigaya Hp., 666; T Satow, K Iihara, T Okazaki, K Morita, H Yamagami, K Ito, S Sugata, M Hayakawa, T Matsushige, D Ishii, T Ishikawa, K Fukuda, K Masuda, T Hashimoto, Y Miyazaki, E Hamano, D Maruyama, N Nakajima, H Okumura, N Funatsu, National Cerebral and Cardiovascular Center, 666; S Yoshimura, J Kokuzawa, Y Enomoto, Y Yoshida, Y Egashira, T Takagi, K Yamada, M Ishiguro, M Tsujimoto, H Watarai, K Yamauchi, H Kitajima, Gifu Univ., 644; H Ishihara, F Oka, T Oku, Yamaguchi Univ., 609; A Kumasaka, K Harada, J Morioka, Fukuoka Wajiro Hp., 601; I Hattori, M Morimoto, S Ozaki, S Kobanawa, M Sasaki, Y Matsumaru, Yokohama Shintoshin Neurosurgical Hp., 598; K Kawaguchi, M Kawanishi, A Shindo, N Hayashi, K Kawakita, T Yano, T Inukai, M Okauchi, Kagawa Univ., 513; T Kuroiwa, F Shimizu, M Shirakawa, H Oonishi, Shimizu Hp., 505; T Nakahara, K Yamashita, H Ohta, I Kamata, H Araki, R Ogami, Matsuda Hp., 488; T Hatano, A Ishii, H Hasegawa, T Kunieda, M Lohanagi, Y Yakenobu, K Yoshida, E Ogino, T Kikuchi, K Takemoto, N Yamana, M Goto, T Munemitsu, Y Yokoyama, H Chihara, Y Mineharu, M Ando, M Saiki, Y Sekihara, N Murai, Y Yamao, H Ikeda, H Hayashi, T Waro, S Satoh, D Arai, N Sakai, Kyoto Univ., 487; M Nakamura, T Mizobe, Hyogo Brain and Heart Center, 484; S Miyachi, I Ikushima, T Izumi, N Matsubara, K Haraguchi, T Makiuchi, K Hashimoto, T Asai, Nagoya Univ., 478; T Hyogo, T Kataoka, T Ogino, H Endo, Nakamura Memorial Hp., 451; K Imai, T Takegami, M Hamanaka, T Yamada, Japanese Redcross Kyoto Daiichi Hp., 433; N Ikeda, Ube-Kohsan Central Hp., 396; T Okamoto, T Kano, H Toi, S Matsubara, Kawasaki Medical School Hp., 395; K Muraio, K Nakazawa, A Takahashi, N Nakajima, Y Iwamuro, T Ohta, S Aketa, N Takabatake, T Kunieda, H Fukuda, K Takemoto, K Miyake, J Morioka, H Yukawa, T Akiyama, Shiroyama Hp., 383; H Konno, K Nakahara, M Nishio, H Hiramatsu, K Shibantai, Japanese Redcross Hachinohe Hp., 375; A Nishio, S Yamauchi, K Kondo, K Haraguchi, K Hayasaki, Y Mitsushashi, T Kawakami, S Yamauchi, A Mizuguchi, K Demura, T Hishikawa, Hokuto Hp., 365; K Satoh, M Hanaoka, S Manabe, T Tamura, T Kinouchi, J Tsurukiri, Y Fukushima, Japanese Redcross Tokushima Hp., 365; N Horie, M Morikawa, K Hayashi, T Higashi, Y Morofuji, Nagasaki Univ., 364; Y Nakai, S Irie, W Tsuruta, T Takigawa, Y Matsumaru, M Sato, G Ikeda, Tsukuba Univ., 363; K Nakazawa, J Ayabe, Yokohama Kyosai Hp., 357; K Akaji, T Iwai, I Naito,

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Address reprint requests to: Nobuyuki Sakai, MD, DMSc, Department of Neurosurgery, Kobe City Medical Center General Hospital, 2-1-1 Minatojima Minaminachi Chuo, Kobe, Hyogo 650-0047, Japan.
e-mail: n.sakai@siren.ocn.ne.jp